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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,308	08/21/2003	Paul B. J. Burton	3432-US-NP	9578

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EXAMINER	
JIANG, DONG	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,308	BURTON ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-62* is/are pending in the application.

4a) Of the above claim(s) *31-45,53 and 55-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-52 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *31-62* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/23/04 & 6/25/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's election without traverse of Invention II filed on 27 September 2007 is acknowledged. Applicant's species elections of a soluble 4-1BB, cardiomyopathy, and doxorubicin filed on 27 September 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Currently, claims 31-62 are pending, and claims 46-52 and 54 are under consideration. Claims 31-45, 53 and 55-62 are withdrawn from further consideration as being drawn to a non-elected invention.

Formal Matters:

Information Disclosure Statement

Applicant's IDSs submitted on 9/23/04 and 6/25/04 are acknowledged and have been considered. A signed copy is attached hereto.

Priority acknowledgement

This application claims benefit of U.S. provisional applications 60/494,457 filed on 8/12/03, and 60/406,418 filed on 8/28/02, which is acknowledged.

Specification

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are directed.

Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 recites the limitation "*the* therapeutically effective amount" in line 1. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claim 54 is directed to a method of treatment for reducing chronic cardiotoxicity of a chemotherapeutic agent with an effective amount sufficient to reduce apoptosis in cardiac tissue of the subject being treated. The specification teaches, in an experimental animal model (Example 8), that apoptosis in cardiac tissue was determined by TUNEL positivity from collected heart, indicating that animals were sacrificed. Given the nature of the invention, a method of treatment, it would not be an option to kill the subject being treated, or even just to take biopsy samples of the sickened heart in order to determine such an effective amount or the effectiveness of the treatment. Therefore, one skilled in the art would not be able to use the claimed invention.

Claims 46-49, 52 and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 46 recites "a 4-1BB antagonist" without specific structure limitation, which reads on any or all functional equivalents. Thus, the claims are drawn to a genus of molecules, which is defined only by functional limitation, and thus, encompasses extreme structural dissimilarity.

For example, it can include nucleic acids, peptide mimetic of an antibody, or small chemical molecules. However, the specification teaches or the prior art has established three types of 4-1BB antagonists, namely, a soluble 4-1BB, an antibody for 4-1BB, and an antibody for 4-1BB-L, and no other "4-1BB antagonist" meeting the limitations of the claim is identified or particularly described.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a functional characteristic, antagonizing 4-1BB. There is no structural identification of any kind for the encompassed molecules. Thus, with the exception of a soluble 4-1BB, an antibody for 4-1BB, and an antibody for 4-1BB-L, the skilled artisan cannot envision the detailed chemical structure of the encompassed "4-1BB antagonist", and therefore conception is not achieved regardless of the complexity or simplicity of the method of making a peptide or chemical molecule. Accordingly, the specification does not provide adequate written description of the claimed genus.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, in the instant case, only the three types of 4-1BB antagonists mentioned above, but not the full breadth of the claims ("a 4-1BB antagonist") meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 46-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yudestad et al. (Cardiovasc Res., 2002 Apr; 54(1):175-82, provided by applicants), and Goodwin et al. (US5,674,704, provided by applicants), and in view of Waelti (US2004/0028687).

Yudestad teaches that it has been reported that elevated circulating levels of inflammatory cytokines such as TNFα, IL-6 and IL-1 in chronic heart failure (CHF) in direct relation to the clinical severity of the disease, that inflammatory cytokines have been shown to induce pathological events in CSF, for example, overexpression of TNFα or infusion of TNFα has been shown to cause a dilated cardiomyopathy-like phenotype mimicking several aspects of clinical heart failure, indicating that both circulating and locally produced cytokines may induce myocardial dysfunction (page 175, the paragraph bridging the two columns). Further, Yudestad

discloses that there is increased gene expression of several TNF superfamily ligands in PBMC of patients with chronic heart failure, including, among others, 4-1BB-L; that in particular, the enhanced expression of ligands in the TNF superfamily may reflect a potential pathogenic role of these cytokines in the progression of CHF (abstract); that enhanced expression of several ligands in the TNF superfamily in PBMC infiltrating the failing myocardium may contribute to the development of myocardial failure, which may in turn lead to further activation of leukocytes within the myocardial circulation, representing a vicious circle in the pathogenesis of CHF (page 181, lines 15-22); and that whereas there is strong evidence for TNFα as a pathogenic factor in CHF, other members of the TNF superfamily may potentially be even more important (page 176, lines 6-9 of the 1st column). Yudestad does not teach to treat cardiomyopathy caused by a chemotherapeutic agent such as doxorubicin with a 4-1BB antagonist such as a soluble 4-1BB protein.

Goodwin teaches soluble 4-1BB polypeptides, which retain the ability to bind the 4-1BB ligand (column 4, lines 23-28); and fusion proteins thereof comprising a soluble 4-1BB and the constant region of an antibody (the paragraph bridging columns 5 and 6). Further, Goodwin teaches soluble forms of 4-1BB proteins are advantageous for certain applications, such as being administered intravenously for therapeutic purposes (column 4, lines 53-56).

Waelti teaches that one of the greatest limitations of cancer chemotherapy are the severe side effects accompanying the use of some of the most broadly active antitumor agents, for example, anthracycline compounds, such as doxorubicin, have a very wide spectrum of anticancer activity, but their side effects include, among others, dose-dependent cardiotoxicity often resulting in irreversible cardiomyopathy with serious congestive heart failure ([0022], bridging pages 2 and 3).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to try to use Goodwin's soluble 4-1BB fusion for the treatment of cardiomyopathy/CHF caused by anthracycline compounds such as doxorubicin (taught by Waelti), as Yudestad teaches that 4-1BB-L, a member of the TNF superfamily, is overexpressed in CHF patients; that TNFα is a pathogenic factor in CHF, and other members of the TNF superfamily may potentially be even more important; and that the enhanced expression of

ligands in the TNF superfamily may reflect a potential pathogenic role of these cytokines in CHF. Therefore, a person with ordinary skill has good reason to pursue the known options within his or her technical grasp. The person of ordinary skill in the art would have been motivated to do so for disease treatment, and reasonably would have expected success because Goodwin has teaches that the soluble 4-1BB retains the ability to bind the 4-1BB ligand, therefore, it would prohibit the binding of the 4-1BB ligand to its receptor, and is a 4-1BB antagonist.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Dong Jiang, Ph.D.
Patent Examiner
AU1646
11/8/07